UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,105	02/27/2004	Claire Trelford Roberts	LP-02-019	7714

7590 09/14/2006

Francis Law Group
1942 Embarcadero
Oakland, CA 94606

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/789,105	ROBERTS ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *8-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Formal Matters

Applicants' amendment filed 23 June 2006 is acknowledged. Claims 1-7 are amended. Claims 18-29 are new. Claims 8-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions.

The text of those sections of 35 U.S.C. not included in this action can be found in a prior office action mailed 29 December 2005.

Objections/Rejections Withdrawn

Oath/Declaration

The objection to the declaration under 37 C.F.R. 1.67(a) as set forth at p. 2 of the Office action mailed 29 December 2006 is withdrawn in response to Applicants' submission of a corrected declaration indicating that the instant application is a continuation of PCT/AU02/01226.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 1-7 under 35 U.S.C. 112, second paragraph for indefiniteness (because the method steps fail to achieve the goal set forth in the preamble) as set forth at p. 3 of the Office action mailed 29 December 2005 is

withdrawn in response to Applicants' amendment of the claims in the response filed 23 June 2006.

Claim Rejections - 35 USC § 102

The rejection of claims 4-6 under 35 U.S.C. 102(b) as being anticipated by O'Neill (Biol Reprod. 1997. 56: 229-237) as set forth at p. 6 of the prior office action (mailed 29 December 2005) has been withdrawn in response to Applicants' amendment of those claims to explicitly recite administration of IGF-II to a female mammal and the method of delivery by vaginal pessary in claim 5 in the amendment filed 23 June 2006.

The rejection of claims 1, 2, 4, 5, 7 under 35 U.S.C. 102(b) for being anticipated by Gluckman et al. (Patent No.5,420,111) as set forth at p. 6 of the prior Office action (mailed 29 December 2005) has been withdrawn in response to Applicants' amendment of those claims. Specifically the method steps complete the goals of the preamble, thus the claims no longer read on administration of IGF-II for any purpose.

Rejections Maintained/New Rejections

Claim Objections

Claim 26 is objected to because of the following informalities: The claim recites IOF-I and JGF-II in the last line, which are presumably typographical errors and should recite "IGF-I" and "IGF-II", respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

Claims 24-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly added independent claims 24-29 do not recite what the effective amount of the differentiation factor is supposed to achieve, thus the method steps do not complete the goal of the preamble. The claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant (see MPEP 2171). For the purposes of prior art, the claims read on the administration of IGF-II to a pregnant female mammal (claims 24, 25, 26) or an embryo (claims 27, 28, 29) for any purpose.

Claim Rejections - 35 USC § 112, first paragraph

The rejection of claims 1-5, 7 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement is maintained for reasons of record and the following. In addition, newly added claims 18-23, 25-29 are also rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicants argue at p. 9, 4th through p. 10, 3rd paragraphs that IGF-II administered alone competes with latent TGF-β in vitro (Example 1), inhibits activation of latent TGF-β in vitro (Example 2) and increase fetal weight, placental thickness and the ratio of fetal weight to placental weight (Example 4).

Applicants argue at p. 10, 2nd paragraph through 4th paragraph that one of ordinary skill in the art would be able to select the appropriate in vitro conditions for the use of precursors, isomers and analogs of IGF-II.

Applicants argue at p. 10, 5th paragraph through p. 11, 1st full paragraph that it is not necessary for the Applicants to show that IGF-II regulates cytotrophoblast differentiation and migration or promotion of implantation, cite 2164.01 of the MPEP and submit evidence in the form of Gude and colleagues (Thromobosis Research. 2004; 114: 397-407), who teach the importance of trophoblast development in placentation. In addition, Applicants submit Sferruzzi-Perri and colleagues, who teach that IGF-II alone increases placental labyrinth cross section and volume and also reiterate that the administration of IGF-II as described in the specification has been shown to improve placental growth, development, differentiation and migration.

Applicants argue at p. 10, 2nd full paragraph that the that the issue of enablement is whether there is an undue burden of experimentation placed upon one of ordinary skill in the art to practice the invention and that one of ordinary skill in the art would be able to select the appropriate culture conditions to use the invention and recognize that the comments provided in the reference cited by the Examiner (Behr and Wang—cited in prior Office action mailed 29 December 2005) relate to the complex process of in vitro fertilization outcome, which is dependent upon numerous factors, which are not directly related to the invention as claimed.

Applicants submit at p. 11, last paragraph to p. 12 last paragraph that newly added claims 24-29 are also enabled because 1) Example 4 provides guidance regarding suitable concentrations of IGF-II that may be administered to enhance placental growth and/or development, 2) Sferruzzi-Perri and colleagues (referenced above) teach that the administration of IGF-II increases placental labyrinth cross section and volume, 3) specification shows that administration of IGF-II results in improved placental growth, development and differentiation, 4) specification clearly discloses the treatment of embryos to increase the success of implantation and to increase the success of formation of a viable placenta and 5) Example 2 provides a description of the use of exogenous IGF-II to inhibit activation of latent TGF-β in vitro by human TFI skill with suitable in vitro culture and treatment conditions.

Applicants submit at p. 13, 2nd full paragraph that the specification provides clear disclosure directed to two mammals, namely human and mouse and that one having ordinary skill in the art often adapts conditions from one species to another and that

likewise one of ordinary skill in the art would be able to practice the invention with regard to precursors, isomers and analogs of IGF-II.

These arguments have been fully considered but are not found persuasive for the following reasons. First, with regard to the argument that that IGF-II administered alone competes with latent TGF-β in vitro (Example 1), inhibits activation of latent TGF-β in vitro (Example 2) and increase fetal weight, placental thickness and the ratio of fetal weight to placental weight (Example 4), the Examiner takes no issue (and took no issue in the prior Office action). The issue was that while the data showed the following: treatment of pregnant mice with IGF-II between days 2 and 10 of pregnancy increased placental weight at day 18 of gestation (FIG. 5); the percentage of placentas that weighed more than 120 mg was 3.1% in control mice, 25.8% in mice treated with the 12.5 μg/day IGF-II, ($p<0.0001$) and 29.8% in mice treated with the 25 μg/day IGF-II ($p<0.0001$) (FIG. 6); treatment of the dam with slow release IGF-II during the first half of pregnancy enhances placental growth; treatment with 25 μg/day IGF-II increased fetal weight by 4.1% ($p<0.05$) (FIG. 7); the distribution of fetal weights across litters was skewed to the right by treatment with IGF-II; the percentage of fetuses weighing more than 1100 mg was 21.5% in control mice, 27.4% in mice treated with 12.5 μg/day IGF-II (NS) and 53.6% in mice treated with the 25 μg/day IGF-II ($p<0.0001$) (FIG. 8), they did not necessarily support the intended use in the preamble, namely that the method was for regulating cytotrophoblast differentiation. Applicants have amended the claims to recite "[a] method of inhibiting proteolytic conversion of inactive TGF-β to active TGF-β to by a CIM6P receptor on a cytotrophoblast cell...," thus introducing a new preamble

into the claim. If the preamble of the claim states the goal or intended use of the method, the specification must enable that intended use. Example 2 and Figure 2 show that the addition of IGF-II to the culture media decreases the percentage over control of active TGF-β. However, the data do not provide evidence that this is accomplished by inhibition of proteolytic conversion of inactive TGF-β to active TGF-β by a CIM6P receptor. The data do not demonstrate that this inhibition is caused by the CIM6P receptor. Applicants disclose at p. 17, lines 24-26 that when "uPA is omitted from the culture media there is no activation of latent TGF-1...provides further evidence that it is the uPA/uPAR/CIM6P receptor system which is responsible for activation of latent TGF on the cell surface." Furthermore, at [0015], Applicants disclose that it "is known that binding of latent TGF to the CIM6P receptor leads to the production of active TGF by the urokinase plasminogen activator (uPA) system...It is suggested that IGF-II prevents activation of latent TGF." These statements do not provide evidence to support the intended use of the claim. In the absence of a teaching in the specification, it is appropriate to look for support for enablement in the literature. Applicants have amended the preamble or intended use to recite, "[a] method of inhibiting proteolytic conversion of inactive TGF-β by a...CIM6P receptor expressed on a cytotrophoblast line..." A search in the literature databases for IGF-II and CIM6P and TGF-β revealed a paper discerning the crystalline structure of the CIM6P receptor (see entire reference—Olson et al. The EMBO Journal. 2004; 23: 2019-2028) and a paper that the actions of latent pro-TGF-β were reversed by two ligands of the CIM6P receptor, namely beta-galactosidase and a CIM6P antibody (see abstract—Villevalois-Cam et al. Journal of

hepatology. 2003: 38: 156-163), however neither of these references support the intended use of the amended claim 1.

Furthermore, the additional recitation in claims 2 ("wherein said administration of said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type) is not enabled. Nothing in the specification or the literature suggest that the recited (and now expanded) "differentiation factors" could inhibit a cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type. The specification does show that IGF-II treatment between days 2 and 10 of pregnancy (in mice) significantly increased placental weight at day 18 of gestation and presumably placental growth, thus the statements in claim 6 regarding improving placental growth and development are enabled. The data regarding the outcome of treatment with IGF-II are compelling, but they do not support the preambles/intended use in claims 1 and 2 at all. Finally, the Applicants have now expanded the claims beyond the scope of IGF-II or the analog of IGF-II taught in the specification (Leu^{27}IGF-II) and now encompass precursors and isomers of IGF-II, which are not enabled by the disclosure or the literature.

Second, with regard to the argument that one of ordinary skill in the art would be able to select the appropriate in vitro conditions for the use of precursors, isomers and analogs of IGF-II; the Examiner does not take issue that the person of ordinary skill in the art would be able to select the appropriate in vitro conditions for the use of IGF-II and the analog taught in the specification, Leu^{27}IGF-II, however Applicants have vastly

expanded the scope of the claims to encompass precursors and isomers of IGF-II, which finds no support in the specification or the literature. Isomers and precursors of IGF-II are not necessarily going to have the same biological actions as IGF-II. The problem of predicting protein of ascertaining the functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Applicant has provided little or no guidance beyond the mere recitation of isomers or precursors of IGF-II to enable one of ordinary skill in the art to determine, without undue experimentation, which proteins would be capable of carrying out the intended use of the claim. The broad recitation is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Third, with regard to the argument that it is not necessary for the Applicants to show that IGF-II regulates cytotrophoblast differentiation and migration or promotion of implantation (Applicants also cite 2164.01 of the MPEP), this is true insomuch as Applicant has now amended claim 1 to omit the previous recitation of "regulating cytotrophoblast differentiation and migration." However, as stated above, claim 1

recites a single intended use for the method, namely "inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by CIM6P receptor expressed on cytotrophoblast cell," and as stated above, neither the specification nor the literature support this intended use. Furthermore, the amended claim 2 contains statements that are not supported in the specification or the literature (see arguments above).

Fourth, regarding the evidence submitted in the form of Gude and colleagues (Thromobosis Research. 2004; 114: 397-407), who teach the importance of trophoblast development in placentation, the Examiner takes no issue with this. Nevertheless Gude et al. do not provide evidence of a nexus between IGF-II treatment and the intended use recited in claims 1 and 2 (see arguments above). Fifth, with regard to the evidence submitted by Sferruzzi-Perri and colleagues, who teach that IGF-II alone increases placental labyrinth cross section, again, the Examiner takes no issue with this statement, but the claims contain intended use phrases not supported by this reference (see arguments above). Finally, although the specification has been shown to improve placental growth and presumably development as pointed out by both the Examiner (in the prior Office action mailed 29 December 2005) and Applicants, the issue is still that the intended uses recited in the claims are not enabled by the specification or the literature.

Sixth, with regard to Applicants argument that the issue of enablement is whether there is an undue burden of experimentation placed upon one of ordinary skill in the art to practice the invention and that one of ordinary skill in the art would be able to select the appropriate culture conditions to use the invention, which are not directly related to

the invention as claimed, there are additional factors taken under consideration when deciding whether claims are enabled; they are:

(a) the breadth of the claims

(b) the nature of the invention

(c) the state of the prior art

(d) the level of one of ordinary skill

(e) the level of predictability in the art

(f) the amount of direction provided by the inventor

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the present case, the issues raised in the prior Office action and by the amendments to the claims are the complex nature of the invention, the state of the prior art and the level of predictability, the amount of direction provided by inventor, what the working examples teach, the quantity of experimentation needed to use the invention, and now additionally the breadth of the claims introduced by the amendment to the claims which expand the scope of the differentiation factors and the addition of new method goals.

Seventh, with regard to the comments that the reference provided and cited by the Examiner (Behr and Wang—cited in prior Office action mailed 29 December 2005) relate to the complex process of in vitro fertilization outcome, which is dependent upon numerous factors, the Examiner takes no issue with this statement. In fact, the reference was cited by Examiner to support that very point, namely, that it was known in

the art that the complex processes involved with in vitro fertilization outcome was dependent on numerous factors and to demonstrate the goals of the original claims were not enabled by the literature. The teachings of Behr and Wang are particularly pertinent to claims 1-3, 21-23 and 27-29, which encompass treatment of an embryo (either implicitly or explicitly) produced by in vitro fertilization. Behr and Wang show that the state of the art regarding in vitro fertilization is highly unpredictable.

Eighth, with regard to Applicants argument that the specification provides clear disclosure and is directed to two mammals, namely human and mouse and that one having ordinary skill in the art often adapts conditions from one species to another and that likewise one of ordinary skill in the art would be able to practice the invention with regard to precursors, isomers and analogs of IGF-II, this argument is not persuasive. As stated in the prior Office action (mailed 29 December 2005), the working examples show that ***IGF-II*** treatment between days 2 and 10 of pregnancy (in mice) significantly increased placental weight at day 18 of gestation and presumably placental growth and while one of ordinary skill in the art may adapt conditions from one species to another, Applicants have further expanded the scope of the differentiation factors in such a way that is not commensurate with the disclosure or what is known in the prior art (see arguments above regarding unpredictability of substituting different proteins to achieve the same functional effects).

Ninth, with regard to Applicants assertion that newly added independent claims 25-29 are also enabled because 1) Example 4 provides guidance regarding suitable concentrations of IGF-II that may be administered to enhance placental growth and/or

development, 2) Sferruzzi-Perri and colleagues (referenced above) teach that the administration of IGF-II increases placental labyrinth cross section and volume, 3) specification shows that administration of IGF-II results in improved placental growth, development and differentiation, 4) specification clearly discloses the treatment of embryos to increase the success of implantation and to increase the success of formation of a viable placenta and 5) Example 2 provides a description of the use of exogenous IGF-II to inhibit activation of latent TGF-β in vitro by human TF1 skill with suitable in vitro culture and treatment conditions, these arguments are not persuasive for the following reasons. Newly added claim 25 is drawn to a method of promoting implantation of an embryo into the uterine endometrium in a female mammal, comprising administering to said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, and isomer of IGF-II and an analog of IGF-II." As stated by the Examiner in the prior Office action (mailed 29 December 2005), the data presented by Applicant in the specification teach that treatment of pregnant mice between days 2 – 10 of pregnancy increased placental weight at day 18 of gestation, thus treatment of the dam with slow release IGF-II during the first half of pregnancy enhances placental growth and fetal weights across litters was skewed to the right by treatment with IGF-II, however the data only suggest that treatment with IGF-II during the first half of pregnancy increases placental and birth weight, which does not mean that administration of IGF-II would promote implantation into the uterine wall; an event that occurs ***before*** placentation. Newly added claim 26 recites a method of "minimizing a condition selected from the group consisting of

implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption comprising administering..." differentiation factors recited above. The data presented by Applicant do not support minimizing any of the conditions recited in the claim. Similarly amended claims 4, 5 and 7 and newly added dependent claims 18, 19 and 20 are drawn to methods of administering IGF-II to a pregnant female mammal for the intention of inhibiting proteolytic conversion of inactive TFGF-β to active TGF-β (claim 4), promoting implantation and migratory behavior of an embryo (claim 19), minimizing infertility, implantation failure, miscarriage, pre-eclampsia, placental abruption (claim 20) and are not enabled by the disclosure. Furthermore, the data presented by Applicants in the disclosure suggest only that treatment with IGF-II during the first half of pregnancy increases placental and birth weight. Finally, while the specification does provide evidence that IGF-II administration to a pregnant mouse in the first half of pregnancy improved placental growth and development, Applicant has further broadened the scope of said "differentiation factor[s]," in such a way that is not commensurate with the disclosure or what is known in the prior art (see arguments above regarding unpredictability of substituting different proteins to achieve the same functional effects).

Furthermore, with regard to claims 4, 7, 18, 19, 20, 24, 25 and 26, these claims omit essential steps, namely, at what point during pregnancy should the IGF-II be administered? The specification discloses administration of IGF-II to a pregnant mouse during days 2 – 10 of gestation that results in increased placental weight, thus the evidence disclosed by Applicants in their specification suggests that IGF-II is to be

administered during the first half of pregnancy, as is recited in claim 5. There is nothing in the specification or the literature that enables administration of IGF-II during ***any point*** in pregnancy to improve placental growth, development and/or differentiation. IGF-II administered to a pregnant female during the last day of her pregnancy would very likely have no effect on placental growth, development and/or differentiation, however, the claims encompass IGF-II administration on any day of pregnancy.

In the absence of a teaching in the specification, the literature can provide enablement for claimed methods, and indeed some recent findings support IGF-II administration for the support of endometrial differentiation. A review of the literature reveals that IGF-II may be important for endometrial cell function during implantation and pregnancy (Tseng et al. Frontiers in Bioscience. 2002; 7: d1566-d1574—see abstract) and that IGF-II may be important in placental repair or remodeling (Gratton et al. (Placenta. 2002: 23: 303-310—see abstract). On the other hand, IGF-II levels in the peritoneal fluid do not differ significantly among patients with endometriosis and controls, thus suggesting that the IGF-II may not play a role in endometriosis-induced infertility (Kim et al., Fertil. Steril. 2000; 73: 5: 996-1000—see abstract) and IGF-II levels in follicular fluid did not differ between controls and patients with infertility (low ovarian reserve). The literature is silent with respect to the administration of IGF-II for the purpose of treating miscarriage (which can be caused by many different factors), pre-eclampsia, placental abruption or promoting migratory behavior of an embryo, promoting implantation or minimizing implantation failure(claims 19, 20). The preponderance of the evidence suggest that IGF-II levels is not be involved in

endometriosis, endometriosis-induced infertility or general infertility, thus, administration of IGF-II to pregnant females for the purpose of inhibiting proteolytic conversion of inactive TFGF-β to active TGF-β (claim 4), minimizing infertility, miscarriage, pre-eclampsia, implantation failure placental abruption, promoting migratory behavior of an embryo or promoting implantation is not enabled (claims 19, 20). Finally, Applicants have further broadened the scope of the differentiation factors in such a way that is not commensurate with the disclosure or what is known in the prior art (see arguments above regarding unpredictability of substituting different proteins to achieve the same functional effects).

Finally, with regard to claims 3, 21-23 and 27-29, which are drawn to methods of administering IGF-II to an embryo produced by in vitro fertilization (and claims 1-2 encompass treatment of embryos), the issues of enablement are similar to those described in the immediately preceding paragraphs. The goals of the methods recite "improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in a female mammal" (claims 23, 27); promoting implantation of an embryo into the uterine endometrium (claims 21, 28) and "minimizing a condition selected from the group consisting of implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia and placental abruption" (claims 22, 29) as well as "inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by CIM6P receptor expressed on a cytotrophoblast cell", wherein said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type (claims 1-3).

The specification does not provide any support for the goals of the methods of these claims. As stated in the prior Office action (mailed 29 December 2005) and above, the data presented by Applicant in the specification teach that treatment of pregnant mice between days 2 – 10 of pregnancy increased placental weight at day 18 of gestation, thus treatment of the dam with slow release IGF-II during the first half of pregnancy enhances placental growth and fetal weights across litters was skewed to the right by treatment with IGF-II, however the data only suggest that treatment with IGF-II during the first half of pregnancy increases placental and birth weight, which does not necessarily mean that it could treat or improve the conditions recited in the preambles of the claims. As with the immediately preceding paragraph, the literature does suggest that IGF-II may be important for endometrial cell function during implantation and pregnancy (Tseng et al.) and that IGF-II may be important in placental repair or remodeling (Gratton et al). However, the evidence does not suggest that treatment of an ***embryo*** produced for in vitro fertilization with IGF-II may improve placental growth, placental development and placental differentiation, promote implantation and minimize implantation failure. Furthermore, using the same reasoning as applied in the immediately preceding paragraph, the treatment of an embryo produced for in vitro fertilization with IGF-II would not affect miscarriage, recurrent spontaneous miscarriage, pre-eclampsia and placental abruption or inhibit proteolytic conversion of inactive TGF-β to active TGF-β by CIM6P receptor expressed on a cytotrophoblast cell, wherein said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type. Finally,

Applicants have broadened the scope of the differentiation factors in such a way that is not commensurate with the disclosure or what is known in the prior art (see arguments above regarding unpredictability of substituting different proteins to achieve the same functional effects).

In addition, claims 6 and 24 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation comprising administration of IGF-II or Leu^{27}IGF-II to a pregnant female mammal an effective amount of IGF-II in the first half of pregnancy, does not reasonably provide enablement for the methods as broadly claimed.

The claims are drawn to methods for improving placental growth, development and differentiation (claim 6), "improving a characteristic selected from the group consisting of placental growth, placental development, placental differentiation...comprising administering a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, and isomer of IGF-II and an analog of IGF-II". As stated above and in the prior Office action, while the specification does provide evidence that ***IGF-II*** administration to a pregnant mouse in the ***first half*** (days 2 –10) of pregnancy improved placental growth and development, the scope of said "differentiation factor[s]" is not commensurate with the disclosure or what is known in the prior art (see arguments above regarding unpredictability of substituting different

proteins to achieve the same functional effects). Furthermore, these claims omit essential steps, namely, at what point during pregnancy should the IGF-II be administered? Since the specification discloses administration of IGF-II to a pregnant mouse during days 2 – 10 of gestation that results in increased placental weight, the evidence disclosed by Applicants in their specification suggests that IGF-II is to be administered during the first half of pregnancy. There is nothing in the specification or the literature that enables administration of IGF-II during ***any point*** in pregnancy to improve placental growth, development and/or differentiation. IGF-II administered to a pregnant female during the last day of her pregnancy would very likely have no effect on placental growth, development and/or differentiation, however, the claims encompass IGF-II administration on any day of pregnancy. There is also support in the literature for methods improving placental growth, development and differentiation (claims 6, 24). A review of the literature reveals that IGF-II may be important for endometrial cell function during implantation and pregnancy (Tseng et al. Frontiers in Bioscience. 2002; 7: d1566-d1574—see abstract) and that IGF-II may be important in placental repair or remodeling (Gratton et al. (Placenta. 2002: 23: 303-310—see abstract). Nevertheless claims 6 and 24 are not fully enabled for the reasons given above.

Due to the large quantity of experimentation necessary test the infinite number of precursors, isomers or analogs of IGF-II recited in the claims capable of improving placental growth, placental development and placental differentiation, the lack of direction/guidance presented in the specification regarding the ability of the recited

"differentiation factors" to affect miscarriage, recurrent spontaneous miscarriage, pre-eclampsia and placental abruption or inhibit proteolytic conversion of inactive TGF-β to active TGF-β by CIM6P receptor expressed on a cytotrophoblast cell, wherein said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type claims to which are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention (i.e., in vitro fertilization), the unpredictability of administering precursors, isomers or analogs of IGF-II without affecting the outcome of the claimed methods, and the breadth of the claims which fail to recite which precursors, isomers or analogs of IGF-II are capable of improving placental growth, placental development and placental differentiation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 3 under 35 U.S.C. 102(b) as set forth at p. 6 of the prior Office action (mailed 29 December 2005) for being anticipated by O'Neill (Biol Reprod. 1997; 56: 229-237) is maintained for reasons of record and the following. In addition, newly added claims 21-23 and 27-29 are also rejected under 35 U.S.C. 102(b) as being anticipated by O'Neill. The claims recite a method of inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by a CIM6P receptor expressed on a cytotrophoblast cell, comprising administering a differentiation factor selected from the

group consisting of IGF-II a precursor of IGF-II an isomer of IGF-II and an analog of IGF-II in an amount sufficient to promote binding of said differentiation factor to said CIM6P receptor and thereby inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said receptor and thereby inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said receptor, wherein said administration of said differentiation factor inhibits cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type, wherein administration of said differentiation factor to said embryo promotes a result selected from implantation and migratory behavior of an embryo into the uterine endometrium, wherein said differentiation factor is used to minimize infertility, implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclcampsia and placental abruption or improve placental growth development and or differentiation, and wherein said differentiating factor is administered to an embryo produced by in vitro fertilization for implantation into a female mammal. Note that the preambles of claims 27-29, namely, a method of improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in a female mammal (claim 27), promoting implantation of an embryo into the uterine endometrium of a female mammal (claim 28) and minimizing a condition selected from the group consisting of implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in a female mammal (claim 29) are given little patentable weight because the method steps do not complete the goal of the preamble (see above under Rejections under 112, 2).

O'Neill teaches a method of administration of IGF-II to mouse embryos produced by fertilization in vitro. Because O'Neill teaches the ***same methods steps*** as those taught by Applicant, ***namely administration of IGF-II to an embryo produced by in vitro fertilization***, any effects asserted by Applicants in the preambles to the claims (recited in the immediately preceding paragraph) would also inherently be achieved by the method taught by O'Neill. Although O'Neill does not explicitly state that the embryos isolated in the experiments are for implantation into a female mammal, the methods are consistent with the goal of improving the chances of implantation in in vitro fertilization procedures. Furthermore, the claims do not recite a method step wherein the embryo is actually implanted into a female mammal.

Applicants argue at p. 13, last paragraph, p. 14, 3rd and 4th paragraphs that O'Neill does not teach inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by said receptor and thereby inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by said receptor; inhibiting cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type, improving placental growth, placental development and placental differentiation in a female mammal, promoting implantation of an embryo into the uterine endometrium and minimizing implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and/or placental abruption in a female mammal. These arguments have been fully considered but are not persuasive O'Neill teaches the ***same methods steps*** as those taught by Applicant, ***namely administration of IGF-II to an embryo***

produced by in vitro fertilization, any effects asserted by Applicants in the preambles to the claims would also inherently be achieved by the method taught by O'Neill.

Claims 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Gluckman et al (Patent No. 5,420,111). The claims recite a method of improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in a pregnant female (claim 24), promoting implantation of an embryo into the uterine endometrium in a female mammal (claim 25), and minimizing a condition selected from the group consisting of implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in a female mammal (claim 26) comprising administering to a pregnant female mammal IGF-II, a precursor of IGF-II, an isomer of IGF-II or an analog of IGF-II. Note that the preambles are given little patentable weight because the method steps do not complete the goal of the preamble (see above under Rejections under 112, 2), thus the claims encompass administration of IGF-II, a precursor of IGF-II, an isomer of IGF-II or an analog of IGF-II for any purpose.

As stated in the previous Office action, Gluckman et al. teach a method of administration of IGF-II to a pregnant female (see column 3, lines 47-51) at "any time from conception forward."

Applicants argue at p. 14, 5th paragraph to p. 15, 1st 2 lines that Gluckman et al. disclose the administration of IGF-I or IGF-II to improve fetal weight, and that treatment with IGF-I results in a reduction in the negative correlation between mean fetal weight

and litter size and that Gluckman et al. do not teach the claimed differentiation factors to bind the CIM6P receptor and inhibit formation of active TGF-β.

Applicants argue at p. 15, 1st full paragraph that Gluckman et al. merely hypothesizes that IGF-II would act in a similar manner to IGF-I, and that IGF-I would exhibit poor affinity for the CIM6P receptor.

Applicants argue at p. 15, 2nd full paragraph that new independent claims 24-26 are directed to improving placental growth, development, differentiation, promoting implantation, preventing and/or treating a number of conditions recited in claim 26.

Applicants argue at p. 15, 3rd paragraph that O'Neil (sic—presumably Gluckman et al. was intended) disclose that IGF-I does not appear to increase placental size, thus does not disclose the use of the claimed differentiation factor to promote placental growth, development or differentiation and that Gluckman teaches away from the current invention.

These arguments have been fully considered but are not persuasive because, as stated above, the claims as written encompass administration of IGF-II, a precursor of IGF-II, an isomer of IGF-II or an analog of IGF-II for any purpose. Furthermore, Gluckman also says at column 3, lines 45-51: "although the studies to be discussed herein concentrate on the use of IGF-1, the claims extend to IGF-2 and analogues of IGF-1 and IGF-2 as these are known to exert a similar biological effect to IGF-1 (Schoenle et al., Acta Endoc. 108: 167-174, 1985)." Note also that the differentiation factors recited are extremely broad and are not limited to IGF-II.

Claim Rejections - 35 USC § 103

The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable in view of O'Neill for reasons of record. As stated in the prior Office action (mailed 29 December 2006), although O'Neill fails to disclose administration of IGF-II to the specific mammalian embryos recited in claim 7, it would have been obvious to extend the applicability of its teaching from mouse embryos to other mammalian embryos.

Applicants argue at p. 16, 2nd paragraph that the O'Neill reference contains no teaching regarding the use of IGF-II to inhibit proteolytic conversion of inactive TGF-β to active TGF-β by the CIM6P receptor expressed on a cytotrophoblast cell, it fails to suggest the invention of claim 1 and any of its dependents, however as stated above, this argument is not persuasive because O'Neill teaches the ***same methods steps*** as those taught by Applicant, ***namely administration of IGF-II to an embryo produced by in vitro fertilization***, any effects asserted by Applicants in the preambles to the claims would also inherently be achieved by the method taught by O'Neill.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER